

CASE REPORT

Successful Treatment of Pulmonary Hemorrhage Associated with Leptospirosis and Scrub Typhus Coinfection by Early Plasma Exchange

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Leptospirosis and scrub typhus coinfections have been reported in up to 41% of agricultural workers with acute leptospirosis in Thailand, but only sporadically in Taiwan. Because of the nonspecific clinical presentations, it is difficult to differentiate patients with coinfections from leptospirosis alone. However, failure to identify coinfection may lead to mortality if inappropriate antibiotics are used. We report a 31-year-old man coinfecting with leptospirosis and scrub typhus, which manifested as diffuse alveolar hemorrhage and acute renal failure mimicking pulmonary-renal syndrome. The patient was treated by early plasma exchange and a 7-day course of moxifloxacin therapy. Both pulmonary hemorrhage and hypoxemia resolved substantially on the 4th day of hospitalization. He had a complete recovery from the disease after 6 weeks of hospitalization. [*J Formos Med Assoc* 2007;106(2 Suppl):S1–S6]

Key Words: leptospirosis, moxifloxacin, plasma exchange, pulmonary hemorrhage, scrub typhus

Both leptospirosis and scrub typhus are zoonotic infections. Leptospirosis is caused by spirochetes of the species *Leptospira interrogans*. It occurs worldwide with the highest incidence in the tropics. Human infection may be acquired by direct contact with the urine of infected animals or by exposure to contaminated water or soil.¹ Scrub typhus is an endemic disease in eastern Asia and the southwestern Pacific caused by infection with *Orientia tsutsugamushi* transmitted by the bite of larval trombiculid mites (chiggers).² Both diseases have a broad spectrum of clinical manifestations ranging from nonapparent flu-like illness to fulminant fatal disease. Coinfections have been reported in up to 41% of Thai agricultural workers with acute

leptospirosis³ and in sporadic cases in Taiwan.^{4,5} It is difficult to differentiate patients with coinfection from individuals who have leptospirosis alone, while the former appear to have higher platelet counts and lower serum bilirubin and creatinine concentrations. Nonetheless, a severe coinfection may lead to mortality if inappropriate antibiotics are used.³ Here, we report a case coinfecting with leptospirosis and scrub typhus manifesting as diffuse alveolar hemorrhage and acute renal failure mimicking pulmonary-renal syndrome. A brief review of the literature on the role of plasma exchange, glucocorticoid pulse therapy, and moxifloxacin therapy is also included.

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Case Report

In May 2005, a 31-year-old abattoir worker suffering from fever and chills for 3 days was admitted to the emergency department. On arrival, he complained of multiple constitutional symptoms including right upper quadrant abdominal pain, myalgia, nausea, vomiting, productive cough with scanty sputum, and shortness of breath. There was no history of any major systemic disease, though the patient reported smoking cigarettes and occasional alcoholic beverage consumption. He denied recent travel or contact with sick persons, but rodents had been seen at his workplace. His body temperature was 36.6°C, pulse rate 120 beats per minute, respiratory rate 20 times per minute, and blood pressure 79/46 mmHg. Physical examination disclosed conjunctival suffusion without scleral icterus. The neck was supple. Chest auscultation revealed fine crackles over the left lower lung with no cardiac murmur. The abdomen was soft and flat with normoactive bowel sounds. The liver and spleen were not palpable. Tenderness in the right upper quadrant was noted but Murphy's sign was negative. There was no skin rash, petechia, eschar or lymphadenopathy.

Arterial blood gas measurements disclosed pH 7.426, PCO₂ 31.1 mmHg, PO₂ 103.4 mmHg, and HCO₃ 20 mmol/L on 3 L of oxygen per minute by nasal cannula. Complete blood cell count showed leukocytosis (white cell count 12,200 cells/μL, with 87.9% neutrophils, 5.2% lymphocytes, 6.5% monocytes, and 5.2% eosinophils) and thrombocytopenia (platelet count 69,000/μL). Hemoglobin was 13.4 g/dL. The prothrombin time and partial thromboplastin time were within normal limits. Serum blood urea nitrogen was 43 mg/dL, creatinine 4.1 mg/dL, sodium 136 mmol/L, potassium 4.0 mmol/L, and creatine kinase 150 U/L. Serum total bilirubin was 1.3 mg/dL, aspartate aminotransferase 19 U/L, amylase 505 U/L, and lipase 86 U/L. Urinalysis revealed microscopic hematuria, pyuria, and proteinuria. Electrocardiography showed sinus tachycardia. Chest radiography showed slightly increased infiltrations in the left lower lung field (Figure 1).

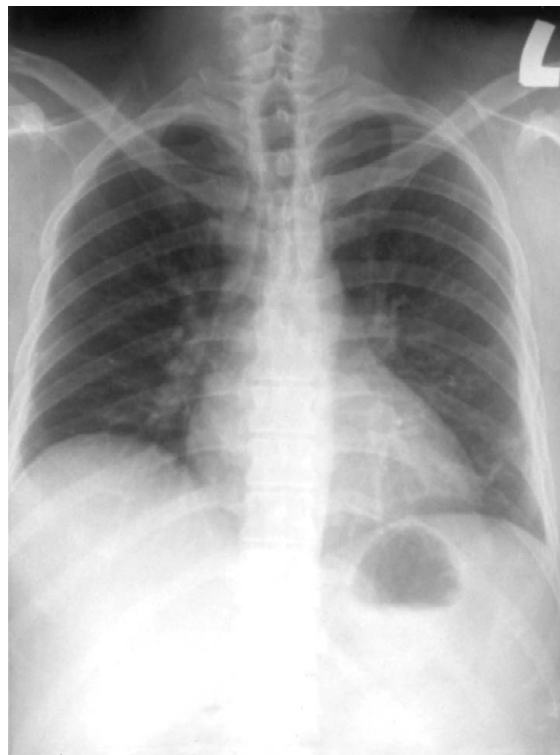


Figure 1. Chest radiograph on admission reveals slightly increased infiltrations in the left lower lung field.

The patient's blood pressure increased to 91/42 mmHg after fluid resuscitation and vasopressor therapy, but high fever up to 40.2°C was noted. Empiric antibiotic therapy with intravenous ampicillin/sulbactam 1.5 g every 6 hours was initiated, and he was admitted to a general ward. Acute hypoxemic respiratory failure and hemodynamic instability developed on the 2nd day of hospitalization. Endotracheal intubation was performed and mechanical ventilation given and the patient was transferred to an intensive care unit. Refractory hypoxemia, acute renal failure, and hemoptysis through the endotracheal tube ensued rapidly. Follow-up chest radiography showed nodular opacities with confluent consolidations throughout bilateral lung fields (Figure 2). Although these clinical manifestations are compatible with pulmonary-renal syndrome, severe leptospirosis or community-acquired pneumonia with acute respiratory distress syndrome and multiple organ failure could not be excluded. Therefore, serologic tests for pulmonary-renal syndrome, leptospirosis, and pathogens associated

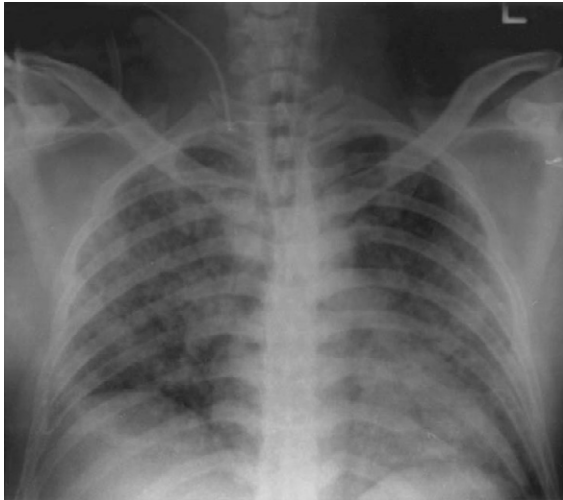


Figure 2. Chest radiograph on the 2nd day of hospitalization shows nodular opacities with confluent consolidations throughout bilateral lung fields.

with hemorrhagic fever were performed, and antibiotics were changed to imipenem/cilastatin 500 mg every 6 hours plus moxifloxacin 400 mg daily. Airway pressure release ventilation was used to improve oxygenation. The patient underwent therapeutic plasma exchange as a standard treatment for Goodpasture's syndrome⁶ due to its potential benefits in patients with severe leptospirosis,⁷ multiple organ failure syndromes,⁸ and other pulmonary-renal syndromes.⁶ During the procedure, one plasma volume was removed and replaced by the same volume of fresh frozen plasma. Steroid pulse therapy with methylprednisolone 1 g/day was started but discontinued within 12 hours because of active upper gastrointestinal bleeding.

Hypoxemia and pulmonary infiltrates resolved substantially on the 4th day of hospitalization (Figure 3). Although serum titers of autoantibodies against glomerular basement membrane, neutrophil cytoplasm, nuclear antigen, and double stranded DNA remained within normal limits, profound jaundice, rhabdomyolysis, and hemolysis were still noted. Severe leptospirosis was highly suspected. Imipenem/cilastatin treatment was stopped in less than 3 days. The patient received eight courses of plasma exchange and 7 days of moxifloxacin therapy. Renal replacement therapy was also arranged for the treatment of oliguric renal

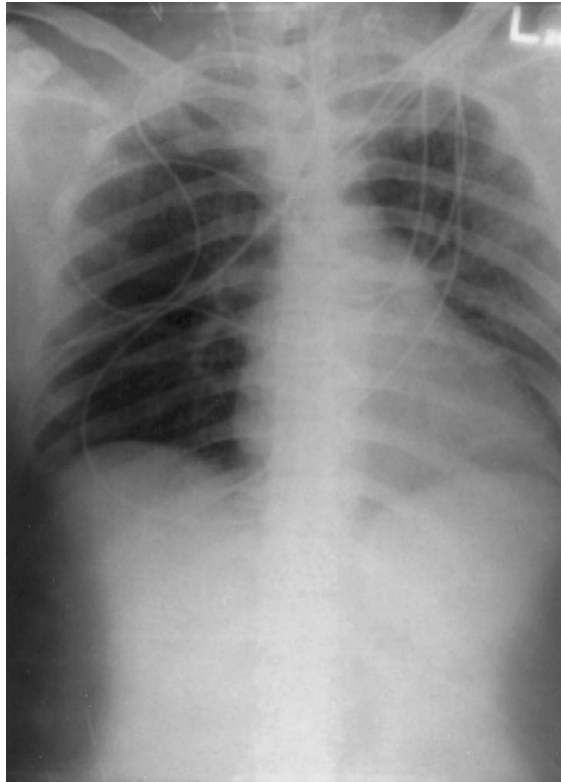


Figure 3. Chest radiograph on the 4th day of hospitalization shows substantial resolution of pulmonary infiltrates.

failure. Renal and hepatic functions recovered thereafter (Figure 4). Reports from the Center for Disease Control in Taiwan indicated that the serologic tests for potential pathogens were all negative on admission. Microscopic agglutination test (MAT) showed a titer of 1:400 for *L. interrogans* serovar Javanica 4 weeks later. Immunofluorescent antibody (IFA) test in paired sera demonstrated a $\geq 1:80$ titer of IgM and a fourfold increase of IgG against *O. tsutsugamushi* as well. The diagnosis of leptospirosis and scrub typhus coinfection was thus confirmed. The patient completely recovered from the disease after 6 weeks of hospitalization.

Discussion

Pulmonary involvement in leptospirosis has become an important issue because its underdiagnosis may lead to a grave prognosis.⁹ Three different clinical forms have been described. The mild to moderate form shows pulmonary infiltrates

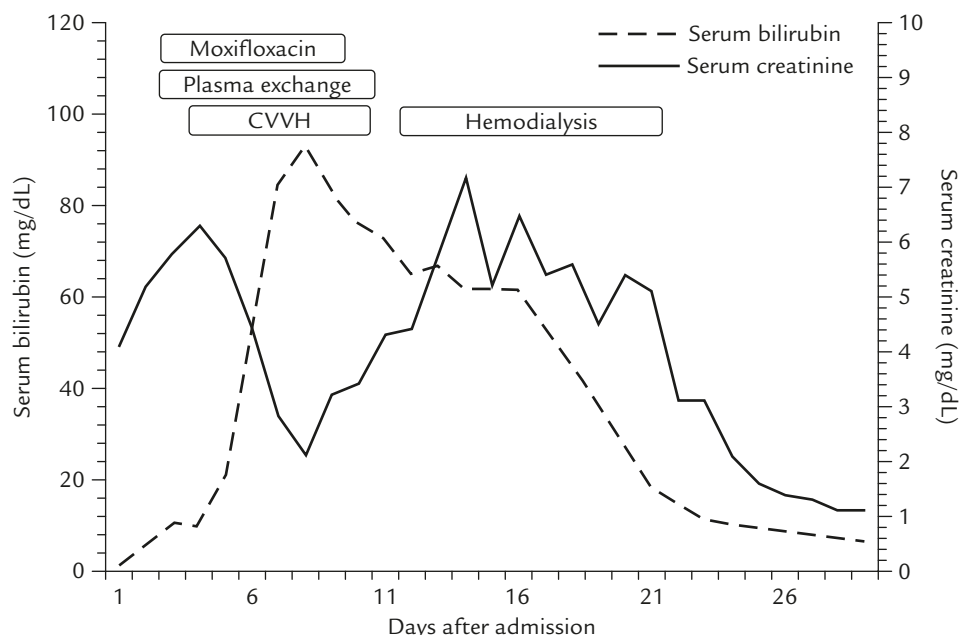


Figure 4. Levels of serum bilirubin and creatinine decreased gradually after antibiotic therapy, plasma exchange, and renal replacement therapy.

associated with minimal alternation of renal function and jaundice. The severe form, also known as Weil's disease, manifests as profound jaundice, acute renal failure, hemorrhagic diathesis, hemoptysis, and occasional cardiovascular collapse. The fulminant form, severe pulmonary hemorrhage syndrome, is frequently fatal without jaundice, nephropathy or other hemorrhages.¹⁰ Recently, leptospirosis presenting with pulmonary hemorrhage has been increasingly reported in Taiwan.^{11,12} In contrast, the serious pulmonary complications of scrub typhus in Taiwan are interstitial pneumonitis and acute respiratory distress syndrome.¹³ No association between scrub typhus and pulmonary hemorrhage has been reported.

The etiology of fatal pulmonary hemorrhage in leptospirosis remains unclear. Development of endothelial damage and vasculitis has been cited as the primary mechanism of leptospirosis-related organ dysfunction.¹ However, linear deposition of immunoglobulin and complement C3 along the alveolar basement membrane was found in parallel with pulmonary hemorrhage in a guinea pig model of severe pulmonary leptospirosis. This pattern is similar to that seen in Goodpasture's syndrome, while examination of renal tissue found

intact glomeruli without focal or segmental glomerulonephrosis characteristic of Goodpasture's syndrome before the development of basement membrane nephropathy.¹⁴ This finding remains unconfirmed in human leptospirosis but suggests a possible role for an autoimmune process.¹⁵

The clinical features of leptospirosis and scrub typhus are mostly nonspecific. The classical triad of Weil's disease, including jaundice, acute renal failure, and hemorrhagic diathesis, represents only the very severe presentation of leptospirosis. The most common symptoms of recognized leptospirosis are fever, myalgia, headache, abdominal pain, and conjunctival suffusion,^{1,16} which are similar to those of viral infections. The presence of an eschar is pathognomonic for scrub typhus, although 40% of cases do not demonstrate this feature.¹³ Fever, headache, rash, myalgia, lymphadenopathy, and hepatosplenomegaly are also observed frequently.²

Since the clinical diagnosis is unreliable, the identification of leptospirosis and scrub typhus relies on laboratory tests. The definitive method for serologic diagnosis of leptospirosis remains the MAT. A single titer of $\geq 1:400$ or a fourfold or greater rise in titer between paired sera confirms

the diagnosis. However, the assay has low sensitivity during the first week of illness.¹ When early diagnosis or serovar typing is imperative, polymerase chain reaction may be helpful. IgM enzyme-linked immunosorbent assay has also been shown to be more sensitive than MAT in the acute phase of the illness.¹⁵ The confirmatory tests of choice for scrub typhus are the IFA test and the indirect immunoperoxidase test. The commercially available Weil–Felix test lacks sensitivity and specificity.²

Prompt and appropriate antibiotic therapy is crucial to the successful treatment of severe leptospirosis and scrub typhus. Intravenous penicillin G is considered to be a drug of choice for severe leptospirosis, although recent trials suggest that treatment with ceftriaxone, cefotaxime or doxycycline has equivalent efficacy.^{17,18} Newer antibiotics, including moxifloxacin and azithromycin, also had excellent *in vitro* activity against some *Leptospira* species.¹⁹ Doxycycline and chloramphenicol are effective in treating scrub typhus,² but resistant strains to both drugs have been reported in northern Thailand.²⁰ Since fluoroquinolone therapy was associated with a favorable outcome in severe scrub typhus, it could be an alternative choice if drug resistance is a concern.²¹ Combination antibiotic therapy with penicillin G plus doxycycline was used frequently for treatment of leptospirosis and scrub typhus coinfection.³ Our experience in this case suggests that moxifloxacin therapy may be effective as well.

The novel therapeutic interventions to remove autoantibodies from blood and reduce their synthesis should be considered as adjuvant therapies in severe leptospirosis complicated with multiple organ dysfunctions.¹² Improved systemic hemodynamics and normalized blood pressure in patients with severe leptospirosis were reported after plasmapheresis or continuous venovenous hemofiltration.²² Plasma exchange may confer beneficial effects by amelioration of the toxic effects of hyperbilirubinemia on hepatocyte and renal tubular cell function.²³ Both of these responses were observed in our patient. High dose glucocorticoid pulse therapy could reduce the

mortality rate of leptospirosis patients with pulmonary involvement when administered early after the onset of dyspnea.²⁴ Randomized controlled studies, however, are required to confirm these results and to define the optimal protocol.

In conclusion, leptospirosis and scrub typhus are frequent causes of acute febrile illness in endemic areas. Because of the nonspecific clinical presentations, coinfection should be considered in patients with either disease who respond poorly to treatment. The present case supports that early plasma exchange is beneficial for the management of pulmonary hemorrhage associated with leptospirosis and scrub typhus coinfection. Moxifloxacin may be an alternative antibiotic choice if coinfection or drug resistance is a concern. The role of high dose glucocorticoid pulse therapy remains to be determined.

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